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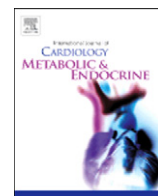
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Untreated diabetes mellitus, but not impaired fasting glucose, is associated with increased left ventricular mass and concentric hypertrophy in an elderly, healthy, Swedish population☆



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ABSTRACT

Background/objectives: To examine whether higher fasting plasma glucose (FPG) levels were independently associated with left ventricular (LV) mass and/or geometry in elderly, otherwise healthy subjects.

Methods: We tested cross-sectional associations between echocardiographically determined LV mass/geometric patterns, cardiovascular risk factors, and FPG categorized as normal fasting glucose (NFG), impaired fasting glucose (IFG), and untreated diabetes mellitus (DM), in 486 men and 207 women aged 56–79 years without overt cardiovascular disease, who received no cardiovascular, anti-diabetic, or lipid-lowering drugs and had a preserved LV ejection fraction >50%.

Results: Unadjusted mean LV mass index (LVMI) was significantly greater among subjects with DM than those without (90 ± 26 g/m² vs. 85 ± 20 g/m², $p = 0.01$), as were both relative wall thickness (RWT) (0.43 ± 0.09 vs. 0.40 ± 0.08 , $p = 0.01$) and prevalence of concentric LV hypertrophy (LVH) (11% vs. 6%, $p = 0.03$). However, only RWT remained significantly associated with the presence of DM after multivariable adjustment ($p = 0.04$). Interaction analyses revealed that greater LVMI/LVH was predominantly associated with higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) among subjects with IFG or DM, but not NFG. **Conclusions:** Subjects with untreated DM had higher values of LVMI and a greater prevalence of concentric LVH, but the associations were not independent of other risk factors. NT-proBNP was primarily associated with greater LV size in subjects with IFG or DM.

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1. Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular morbidity and mortality in subjects both with and

without diabetes mellitus (DM) [1–3]. The increase in cardiovascular risk is directly related to the magnitude of increase in LV mass (LVM) [4,5]. Furthermore, the LV geometric pattern determined by the combination of LV mass index (LVMI) and relative wall thickness (RWT) may

Abbreviations: ANOVA, analysis of variance; ASE, American Society of Echocardiography; BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; DT, E-wave deceleration time; DUST, discrete upper septal thickening; EACVI, European Association of Cardiovascular Imaging; EAE, European Association of Echocardiography; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c} (glycosylated hemoglobin); HDL, high-density lipoprotein; ICD, International Classification of Diseases; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; IVS, interventricular septum thickness; LDL, low-density lipoprotein; LV, left ventricular/left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVID, left ventricular internal diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; MPP, Malmö Preventive Project; MPP-RES, Malmö Preventive Project Re-examination Study; NFG, normal fasting glucose; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OGTT, oral glucose tolerance test; PW, posterior wall thickness; RWT, relative wall thickness; SBP, systolic blood pressure; WHO, World Health Organization.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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provide additional prognostic information beyond assessment of LVM alone [6,7].

The pathogenesis of LVH is presumably multifactorial and driven by both hemodynamic and non-hemodynamic factors [8–13]. LVMI and possibly also RWT are significantly greater among patients with DM than those without, and the case may be the same for subjects with impaired glucose tolerance (IGT) [14–20]. However, only few studies have investigated the association between DM and LVM after adjusting for body size and other traditional risk factors [14–19], and whether a graded association between fasting plasma glucose (FPG) category and LVM and geometry exists, has not been clearly established.

Given these knowledge gaps, a comprehensive evaluation of LV size and geometry and their relation to fasting glucometabolic status is justified and may reveal putative mechanisms for the development of LVH in subjects with impaired glucose metabolism. Therefore, the purpose of this cross-sectional study was: 1) To examine whether worse glucometabolic status (i.e. higher FPG category) was associated with greater LVMI, independently of other hemodynamic and non-hemodynamic risk factors; 2) To describe the association between FPG category and LV geometric pattern based on LVMI and RWT; and 3) To identify other risk factors independently associated with greater LVMI and LV geometric pattern.

2. Methods

2.1. Study population

The study subjects were derived from the Malmö Preventive Project (MPP, 1974–1992, $n = 33,346$), a population-based cohort study with the aim of screening for cardiovascular risk factors, alcohol abuse, and breast cancer among inhabitants of Malmö, Sweden, born 1921–1949 [21]. A re-examination study (MPP-RES, $n = 18,238$) was conducted between 2002 and 2006, during which the participants answered a self-administered questionnaire on lifestyle, medical history, and medication. Blood pressure and pulse rate were recorded twice in the supine position after 5 min of rest (with the values averaged for the analyses), and height, weight, waist and hip circumferences were measured. Moreover, blood samples were drawn after overnight fasting for analysis of plasma glucose, serum lipids, and storage in a biobank. In a subsample of 1792 individuals from MPP-RES, an echocardiography and a 12-lead ECG recording were carried out. These subjects were randomly selected from groups defined by fasting plasma glucose (FPG), with oversampling in groups of subjects with impaired fasting glucose (IFG) and DM, in order to ensure a sufficient number of individuals in each category. Both MPP and MPP-RES were approved by the Ethics Committee of Lund University, Sweden, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Prevalent cardiovascular disease or diabetes mellitus

Subjects with prevalent cardiovascular disease ($n = 300$) and/or those on cardiovascular (incl. antihypertensive) ($n = 864$), anti-diabetic ($n = 329$) or lipid-lowering therapy ($n = 464$) were excluded in the present study (total excluded $n = 1029$). Prevalent cardiovascular disease was defined by the *International Classification of Diseases* (ICD-9 and ICD-10) codes gathered from the Swedish Hospital Discharge Registry as well as local hospital and study registries and encompassed previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, heart failure, stroke, or atrial fibrillation and/or flutter.

2.3. Fasting plasma glucose category

The definitions of normal fasting glucose (NFG), IFG, and DM were based on the *World Health Organization* (WHO) criteria [22]: NFG was

defined as a single FPG ≤ 6.0 mmol/L; IFG was defined as a single FPG between 6.1–6.9 mmol/L, or one measurement 7.0–11.0 mmol/L and a separate measurement ≤ 6.9 mmol/L; and untreated DM was defined as a single FPG ≥ 11.1 mmol/L or two separate measurements ≥ 7.0 mmol/L.

2.4. Echocardiography

Echocardiography was conducted with a 3V2c transducer (Acuson Sequoia, Mountain View, CA) or an S3 transducer (Sonos 5500 Philips, Andover, MA). LV ejection fraction (LVEF) was quantified visually. LVM calculations were based on 2-dimensional linear measurements in the parasternal long-axis view at the tips of the mitral valve leaflets at end-diastole, perpendicular to the long axis of LV. The thickness of the interventricular septum (IVS), LV internal diameter (LVID), and the thickness of the posterior wall (PW) were obtained by placing the calipers on the interface between myocardial wall and cavity and the interface between myocardial wall and pericardium, respectively. LVM was then calculated using the Cube formula recommended by the *American Society of Echocardiography* (ASE) and the *European Association of Cardiovascular Imaging* (EACVI) [23], and indexed for BSA, obtaining LVMI. Cut-off values for LVH were LVMI >95 g/m² in women and >115 g/m² in men, respectively. Relative wall thickness (RWT) was calculated as $(2 \times \text{PW}) / \text{LVID}$, allowing categorization of LV geometry into normal (normal LVMI and RWT ≤ 0.42), concentric remodeling (normal LVMI and RWT > 0.42), eccentric LVH (increased LVMI and RWT ≤ 0.42), and concentric LVH (increased LVMI and RWT > 0.42).

LV diastolic function was assessed in the apical four-chamber view using transmitral pulsed Doppler flow with a 1–3 mm sample volume placed between the tips of the mitral valve leaflets (obtaining E, A, and E-wave deceleration time (DT)) and tissue Doppler imaging with the sample volume positioned within 1 cm of the septal and lateral borders of the mitral annulus (obtaining both septal and lateral \dot{e} and averaging the values for the analyses). A mean of 3–5 cycles was used. The intra- and interobserver variability is reported elsewhere [24]. Diastolic function was graded according to the recommendations of ASE and EACVI (formerly known as the *European Association of Echocardiography*) [25], using age-appropriate cut-off values of septal \dot{e} , lateral \dot{e} , E-wave DT, E/A, and averaged E/ \dot{e} . If septal \dot{e} was ≥ 8 and/or lateral \dot{e} was ≥ 10 , subjects were classified as having normal diastolic function. If septal \dot{e} was < 8 and lateral \dot{e} was < 10 , subjects were classified as having diastolic dysfunction, and the values of E-wave DT, E/A, and E/ \dot{e} were used for grading subjects into grade 1, 2 or 3 diastolic dysfunction (Table 1). If E/ \dot{e} was ≥ 9 and ≤ 12 , subjects were only classified as having either grade 1 or 2 diastolic dysfunction if the values of both E-wave DT and E/A fitted the same category. If E/ \dot{e} ≥ 9 and ≤ 12 , but E/A and E-wave DT were incompatible with each other, subjects were classified as having undetermined diastolic dysfunction [26]. If E/ \dot{e} was > 12 , subjects were classified as having either grade 2 or 3 diastolic dysfunction. Finally, all subjects with E/ \dot{e} < 9 were classified as either normal (E-wave DT < 240 ms and E/A ≥ 0.8) or grade 1 diastolic dysfunction (all other subjects), even if they did not strictly fulfill the primary \dot{e} criteria for normal diastolic function. Subjects with LVEF $\leq 50\%$ were excluded from the present study ($n = 29$). Moreover, 41 subjects were excluded due to missing echocardiographic variables. None of the remaining subjects had severe left-sided valvular stenosis or regurgitation.

2.5. Biomarkers

In the echocardiography subcohort, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was analyzed using an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland) at the Department of Clinical Chemistry, Akershus University Hospital, Lorenskog, Norway.

Table 1
Scheme for grading diastolic dysfunction.

| | Grade 0 (normal) | Grade 1 (mild) | Grade 2 (moderate) | Grade 3 (severe) |
|--------------------------|------------------|----------------|--------------------|------------------|
| Septal \dot{e} (cm/s) | ≥ 8 | < 8 | < 8 | < 8 |
| Lateral \dot{e} (cm/s) | ≥ 10 | < 10 | < 10 | < 10 |
| E-wave DT (ms) | 140–240 | ≥ 240 | 140–240 | < 140 |
| E/A | 0.8–1.5 | < 0.8 | 0.8–1.5 | > 1.5 |
| E/ \dot{e} | < 9 | ≤ 12 | ≥ 9 | ≥ 13 |

2.6. Statistical analysis

Continuous variables were summarized by means and standard deviations (approximately normally distributed variables) and medians and interquartile ranges (IQR) (non-normally distributed variables), whereas categorical variables were presented by frequencies and corresponding percentages. Group-wise comparisons were performed using independent samples t-test, one-way analysis of variance (ANOVA), Mann–Whitney U test, Kruskal–Wallis test, and Pearson's χ^2 -test or Fisher's exact test (depending on cell frequencies), and correlations between LV measurements and diastolic function were tested with Pearson's product moment correlation (r) or Kendall's tau-b (τ). The associations between LVMI (and RWT) and various risk factors were assessed by multivariable linear regression. The associations between LVH (including subtypes of LV geometric pattern) and risk factors were assessed by binary logistic regression. In order to define potential explanatory variables for LVMI and LVH, univariable regressions were applied on the following demographic and clinical variables: age, sex, smoking status, body mass index (BMI), waist circumference, systolic blood pressure (SBP), pulse rate, FPG category, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and NT-proBNP. HDL cholesterol, triglycerides, and NT-proBNP were moderately to highly positively skewed and therefore natural log-transformed before inclusion into the regression models. Statistically (on univariable analyses) and clinically significant variables were included in the final multivariable linear and binary logistic regression models, and stepwise backward selection was applied for adjustment of these models with a stay significance level of 0.20. The significance level for the univariable analyses was 0.05. All statistical analyses were carried out using IBM SPSS Statistics 22 (IBM, Armonk, New York, USA) and Stata/IC 13 (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Characteristics of the study population

After applying the aforementioned exclusion criteria, a study cohort of 693 subjects (486 men and 207 women) was left for analysis (Fig. 1), including 346 individuals with NFG, 242 with IFG, and 105 with untreated DM. Subjects were middle-aged or elderly with a median age of 66 (IQR 60–70) years and mildly hypertensive with a mean systolic blood pressure of 147 ± 20 mm Hg. Mean BMI was 23.9 ± 3.2 kg/m², and values of total and LDL cholesterol were 5.9 ± 1.0 mmol/L and 3.9 ± 0.9 mmol/L, respectively. Mean LVMI was 86 ± 21 g/m² (88 ± 22 for men, 80 ± 17 for women), and 13% (10% men, 19% women) fulfilled the gender-specific criteria for LVH (6% eccentric and 7% concentric, respectively). Moreover, 18% (when excluding the 29 subjects with undetermined diastolic dysfunction) had grade 2 or 3 diastolic dysfunction. As shown in Table 2a, higher FPG category was associated with higher BMI, waist circumference, SBP, pulse rate, triglycerides, LVM, and lower HDL cholesterol, whereas the presence of DM was associated with greater values of IVS, PW, RWT, LVMI, male sex, a greater prevalence of grade 2 or 3 diastolic dysfunction, and lower values of LVEF. Table 2b shows the baseline characteristics of the subjects categorized according to LV geometry.

3.2. Determinants of left ventricular mass

3.2.1. Determinants of left ventricular mass index

LVMI was significantly higher in subjects with DM than those without (90 ± 26 g/m² vs. 85 ± 20 g/m², $p = 0.01$, independent samples t-test), but not significantly different between subjects with IFG vs. NFG (87 ± 21 g/m² vs. 84 ± 19 g/m², $p = 0.08$, independent samples t-test). There was a weak, albeit significant correlation between LVMI and diastolic function ($r = 0.171$, $p < 0.0001$). In univariable analyses, greater values of LVMI were associated with higher age, BMI, waist circumference, SBP, NT-proBNP, lower pulse rate, and male sex, but not the graded FPG category. The adjusted multivariable linear regression model is presented in Table 3a and included all these variables except waist circumference. FPG category was forced into the model and significantly interacted with the association between LVMI and NT-proBNP ($p < 0.0001$). NT-proBNP was only significantly associated with LVMI in subjects with IFG or DM (Fig. 2a).

3.2.2. Determinants of left ventricular hypertrophy

There was no significant difference in the prevalence of LVH between subjects with DM and those without (14% vs. 12%, $p = 0.6$, Pearson's χ^2 -test). There was a weak to moderate significant correlation between LVH and diastolic function ($\tau = 0.185$, $p < 0.0001$). In univariable analyses, the presence of LVH was associated with higher age, BMI, SBP, HDL-cholesterol, NT-proBNP, and female sex. The adjusted binary logistic regression model is presented in Table 3b and included all of these variables except HDL-cholesterol, whereas FPG category was once again forced into the model. FPG category also significantly interacted with the association between LVH and NT-proBNP ($p = 0.01$), and this association was stronger among subjects with IFG or DM (Fig. 2b).

3.3. Determinants of left ventricular geometry

3.3.1. Relative wall thickness

RWT was significantly greater among patients with DM than subjects without (0.43 ± 0.09 vs. 0.40 ± 0.08 , $p = 0.01$, independent samples t-test), but there was no difference between subjects with IFG vs. NFG (0.40 ± 0.09 vs. 0.40 ± 0.08 , $p = 0.99$, independent samples t-test). RWT correlated weakly to moderately with diastolic function ($r = 0.259$, $p < 0.0001$). The multivariable model for RWT prediction is shown in supplemental Table A and included age and BMI, while sex and FPG category were forced into the model. DM, but not IFG, remained significantly associated with greater RWT values, when compared to subjects with NFG. No significant interactions were detected.

3.3.2. Concentric left ventricular remodeling

There was no significant difference in the prevalence of concentric remodeling between subjects with DM and those without (32% vs. 30%, $p = 0.6$, Pearson's χ^2 -test). There was a weak to moderate, but significant correlation between concentric remodeling and diastolic function ($\tau = 0.174$, $p < 0.0001$). The multivariable regression model is presented in supplemental Table B. Concentric remodeling was associated with higher age and BMI. Sex and FPG category were forced into the model. There was a significant interaction between FPG category and age in the prediction of concentric remodeling ($p = 0.02$) (supplemental Figure A).

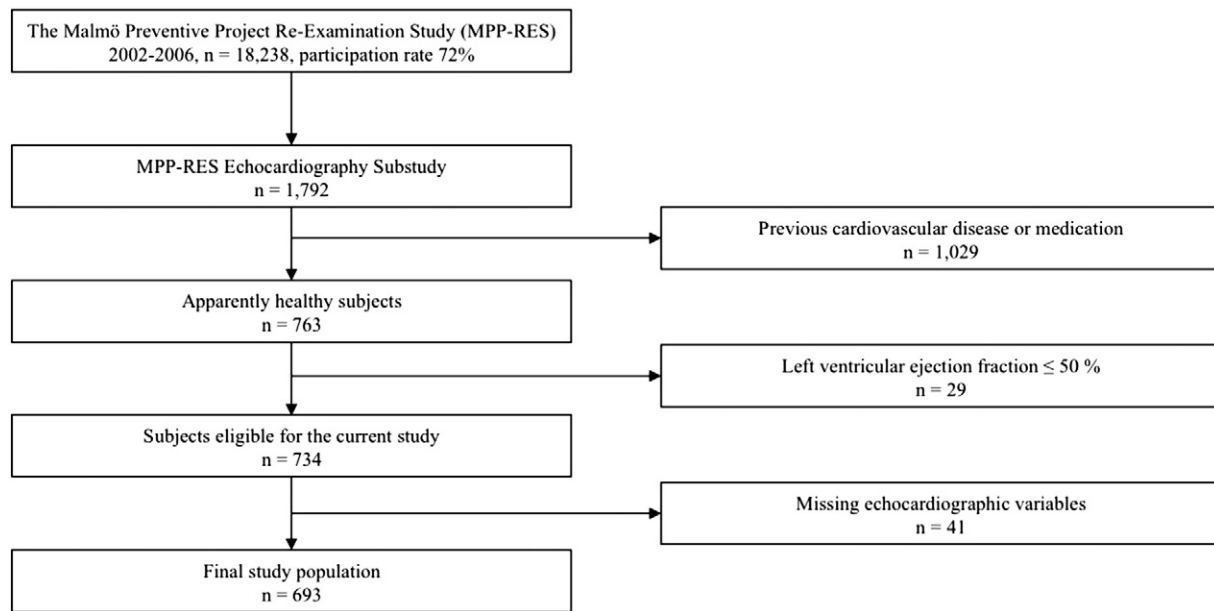


Fig. 1. Flowchart showing the selection of the study population.

3.3.3. Eccentric left ventricular hypertrophy

No statistically significant difference in eccentric LVH was found among subjects with DM compared to those without (3% vs. 7%, $p = 0.2$, Fisher's exact test). There was a weak, but significant correlation between the presence of eccentric LVH and diastolic function ($\tau = 0.145$, $p = 0.002$). The multivariable model for the prediction of eccentric LVH is shown in supplemental Table C and included BMI, NT-proBNP,

triglycerides, and female sex. Age and FPG category were forced into the model. The latter significantly interacted with the association between eccentric LVH and NT-proBNP ($p = 0.04$) (supplemental Figure B).

3.3.4. Concentric left ventricular hypertrophy

Concentric LVH was significantly more prevalent among subjects with DM than those without (11% vs. 6%, $p = 0.03$, Pearson's χ^2 -test),

Table 2a

Baseline characteristics according to fasting plasma glucose category.

| Variable | All subjects (n = 693) | Normal fasting plasma glucose (n = 346) | Impaired fasting plasma glucose (n = 242) | Diabetes mellitus (n = 105) | P-value for difference between FPG categories |
|--------------------------------|---------------------------|--|--|--------------------------------|--|
| Male sex | 486 (70%) | 208 (60%) | 195 (81%) | 83 (79%) | <0.0001 ^a |
| Age (years) | 66 (60–70) | 67 (60–70) | 64 (59–67) | 65 (62–69) | 0.002 ^c |
| Active smoking | 121 (17%) | 54 (16%) | 47 (19%) | 20 (19%) | 0.4 ^a |
| BMI (kg/m ²) | 23.9 ± 3.2 | 23.4 ± 3.0 | 23.9 ± 2.8 | 25.7 ± 3.8 | <0.0001 ^b |
| Waist circumference (cm) | 96 ± 11 | 92 ± 11 | 98 ± 10 | 103 ± 11 | <0.0001 ^b |
| Systolic blood pressure (mmHg) | 147 ± 20 | 143 ± 18 | 150 ± 21 | 155 ± 23 | <0.0001 ^b |
| Pulse rate (beats per minute) | 73 ± 12 | 71 ± 12 | 74 ± 12 | 77 ± 13 | <0.0001 ^b |
| FPG at first visit (mmol/L) | 6.1 (5.4–6.5) | 5.4 (5.1–5.7) | 6.3 (6.2–6.5) | 8.1 (7.4–9.2) | <0.0001 ^c |
| Total cholesterol (mmol/L) | 5.9 ± 1.0 | 5.9 ± 0.9 | 5.9 ± 1.0 | 6.0 ± 1.1 | 0.5 ^b |
| LDL cholesterol (mmol/L) | 3.9 ± 0.9 | 3.9 ± 0.9 | 3.9 ± 0.9 | 4.0 ± 1.0 | 0.5 ^b |
| HDL cholesterol (mmol/L) | 1.3 (1.1–1.6) | 1.4 (1.2–1.7) | 1.3 (1.0–1.5) | 1.1 (0.9–1.3) | <0.0001 ^c |
| Triglycerides (mmol/L) | 1.2 (0.8–1.2) | 1.0 (0.8–1.4) | 1.2 (0.9–1.6) | 1.7 (1.2–2.3) | <0.0001 ^c |
| NT-proBNP (pmol/L) | 8 (5–15) | 10 (5–18) | 7 (4–13) | 9 (6–16) | <0.0001 ^c |
| EF (%) | 62 ± 6 | 62 ± 6 | 61 ± 5 | 61 ± 5 | 0.02 ^b |
| IVS (mm) | 11 ± 2 | 10 ± 2 | 11 ± 2 | 11 ± 2 | <0.001 ^b |
| PW (mm) | 9 ± 1 | 9 ± 1 | 9 ± 2 | 10 ± 2 | <0.001 ^b |
| LVID (mm) | 47 ± 5 | 46 ± 5 | 48 ± 5 | 47 ± 5 | 0.04 ^b |
| RWT | 0.41 ± 0.08 | 0.40 ± 0.08 | 0.40 ± 0.09 | 0.43 ± 0.09 | 0.04 ^b |
| LVM (g) | 166 ± 46 | 158 ± 40 | 172 ± 47 | 180 ± 55 | <0.0001 ^b |
| LVMI (g/m ²) | 86 ± 21 | 84 ± 19 | 87 ± 21 | 90 ± 26 | 0.01 ^b |
| LVH | 88 (13%) | 43 (12%) | 30 (12%) | 15 (14%) | 0.9 ^a |
| LV geometry | | | | | |
| Normal | 397 (57%) | 195 (56%) | 146 (60%) | 56 (53%) | 0.4 ^a |
| Concentric remodeling | 208 (30%) | 108 (31%) | 66 (27%) | 34 (32%) | 0.5 ^a |
| Eccentric hypertrophy | 42 (6%) | 27 (8%) | 12 (5%) | 3 (3%) | 0.1 ^a |
| Concentric hypertrophy | 46 (7%) | 16 (5%) | 18 (7%) | 12 (11%) | 0.04 ^a |
| Diastolic dysfunction | 116 (18%) | 60 (19%) | 29 (13%) | 27 (26%) | 0.01 ^a |

Categorical variables (male sex, active smoking, LVH, LV geometry, grade 2 or 3 diastolic dysfunction) are given as n (%), whereas continuous variables are given as mean ± SD (approximately normally distributed variables, i.e. BMI, waist circumference, SBP, pulse rate, total cholesterol, LDL cholesterol, LVMI, EF, IVS, PW, LVID, RWT, LVM, and LVMI) or median (IQR) (non-normally distributed variables, i.e. age, FPG, HDL cholesterol, triglycerides, and NT-proBNP).

^a Pearson's χ^2 -test.

^b One-way ANOVA.

^c Kruskal–Wallis test.

Table 2b

Baseline characteristics according to LV geometric pattern.

| Variable | Normal geometry (n = 397) | Concentric remodeling (n = 208) | Eccentric LVH (n = 42) | Concentric LVH (n = 46) | P-value for difference between FPG categories |
|--------------------------------|------------------------------|------------------------------------|---------------------------|----------------------------|--|
| Male sex | 297 (75%) | 140 (67%) | 21 (50%) | 28 (61%) | 0.002 ^a |
| Age (years) | 63 (59–67) | 67 (61–70) | 67 (64–70) | 70 (67–74) | <0.0001 ^c |
| Active smoking | 71 (18%) | 36 (17%) | 5 (12%) | 9 (20%) | 0.8 ^a |
| BMI (kg/m ²) | 23.5 ± 2.9 | 24.3 ± 3.3 | 24.6 ± 4.1 | 25.3 ± 3.6 | 0.0001 ^b |
| Waist circumference (cm) | 96 ± 11 | 96 ± 11 | 93 ± 12 | 96 ± 12 | 0.4 ^b |
| Systolic blood pressure (mmHg) | 146 ± 21 | 146 ± 18 | 152 ± 20 | 157 ± 22 | 0.001 ^b |
| Pulse rate (beats per minute) | 73 ± 12 | 73 ± 12 | 70 ± 11 | 74 ± 13 | 0.41 ^b |
| FPG at first visit (mmol/L) | 6.1 (5.4–6.5) | 5.9 (5.4–6.5) | 5.9 (5.4–6.2) | 6.4 (5.6–7.1) | 0.04 ^c |
| Total cholesterol (mmol/L) | 5.9 ± 1.0 | 5.9 ± 1.0 | 6.1 ± 1.0 | 6.0 ± 1.0 | 0.4 ^b |
| LDL cholesterol (mmol/L) | 3.9 ± 0.9 | 3.9 ± 1.0 | 4.1 ± 0.8 | 4.0 ± 1.0 | 0.5 ^b |
| HDL cholesterol (mmol/L) | 1.3 (1.0–1.6) | 1.3 (1.1–1.6) | 1.4 (1.3–1.9) | 1.3 (1.1–1.5) | 0.02 ^c |
| Triglycerides (mmol/L) | 1.2 (0.8–1.7) | 1.2 (0.9–1.7) | 1.0 (0.8–1.1) | 1.2 (0.9–1.5) | 0.04 ^c |
| NT-proBNP (pmol/L) | 7 (4–13) | 9 (5–15) | 17 (7–29) | 16 (8–32) | <0.0001 ^c |
| EF (%) | 61 ± 5 | 63 ± 6 | 61 ± 5 | 64 ± 7 | <0.001 ^b |
| IVS (mm) | 10 ± 2 | 11 ± 2 | 12 ± 2 | 14 ± 2 | <0.0001 ^b |
| PW (mm) | 9 ± 1 | 10 ± 1 | 10 ± 1 | 12 ± 1 | <0.0001 ^b |
| LVID (mm) | 48 ± 4 | 43 ± 4 | 52 ± 4 | 47 ± 5 | <0.0001 ^b |
| RWT | 0.36 ± 0.04 | 0.48 ± 0.06 | 0.38 ± 0.03 | 0.51 ± 0.09 | <0.0001 ^b |
| LVM (g) | 156 ± 35 | 159 ± 36 | 226 ± 65 | 235 ± 50 | <0.0001 ^b |
| LVMI (g/m ²) | 80 ± 15 | 82 ± 15 | 120 ± 27 | 122 ± 17 | <0.0001 ^b |
| Diastolic dysfunction | 45 (12%) | 42 (22%) | 11 (28%) | 18 (40%) | <0.0001 ^a |

Categorical variables (male sex, active smoking, grade 2 or 3 diastolic dysfunction) are given as n (%), whereas continuous variables are given as mean ± SD (approximately normally distributed variables, i.e. BMI, waist circumference, SBP, pulse rate, total cholesterol, LDL cholesterol, LVMI, EF, IVS, PW, LVID, RWT, LVM, and LVMI) or median (IQR) (non-normally distributed variables, i.e. age, FPG, HDL cholesterol, triglycerides, and NT-proBNP).

^a Pearson's χ^2 -test.

^b One-way ANOVA.

^c Kruskal–Wallis test.

but there was no significant difference between subjects with IFG and those with NFG (7% vs. 5%, $p = 0.3$, Pearson's χ^2 -test). The presence of concentric LVH correlated moderately to strongly with diastolic function ($\tau = 0.280$, $p < 0.0001$). The multivariable model is presented in supplemental Table D. Concentric LVH was associated with higher age, BMI, SBP, and NT-proBNP. Sex and FPG category were forced into the model; however, with both IFG and DM as borderline significant predictors of concentric LVH. Furthermore, FPG category significantly interacted with the association between concentric LVH and NT-proBNP ($p = 0.02$) (supplemental Figure C).

4. Discussion

The main findings of our study were: 1) Significantly greater LVMI, RWT, and prevalence of concentric LVH among subjects with untreated DM than those without; 2) significant interactions, i.e. effect modifications, between FPG category and the association between NT-proBNP and LVMI and LVH (incl. eccentric and concentric LVH), respectively, with higher NT-proBNP being predominantly associated with greater LVMI or LVH among patients with IFG or DM.

Table 3aMultivariable linear regression model for the prediction of LVMI (adjusted $r^2 = 0.204$).

| Risk factor | Beta-coefficient (β) (95% CI) | P-value |
|--|--|---------|
| Age (per year) | 0.25 (−0.04 to 0.55) | 0.1 |
| Female sex | −11.03 (−14.49 to −7.57) | <0.0001 |
| Body mass index (per kg/m ²) | 0.91 (0.44 to 1.39) | <0.001 |
| Systolic blood pressure (per mmHg) | 0.20 (0.13 to 0.28) | <0.0001 |
| Pulse rate (per min ^{−1}) | −0.26 (−0.38 to −0.13) | 0.0001 |
| Log(NT-proBNP) (per log(pmol/L)) | 5.59 (3.71 to 7.48) | <0.0001 |
| Fasting plasma glucose (FPG) category | | |
| Normal fasting glucose (NFG) (reference) | | |
| Impaired fasting glucose (IFG) | 1.94 (−1.34 to 5.23) | 0.25 |
| Diabetes mellitus (DM) | 1.17 (−3.26 to 5.61) | 0.6 |

Waist circumference was significantly associated with LVMI in univariable analysis only.

4.1. Demographics and risk factors

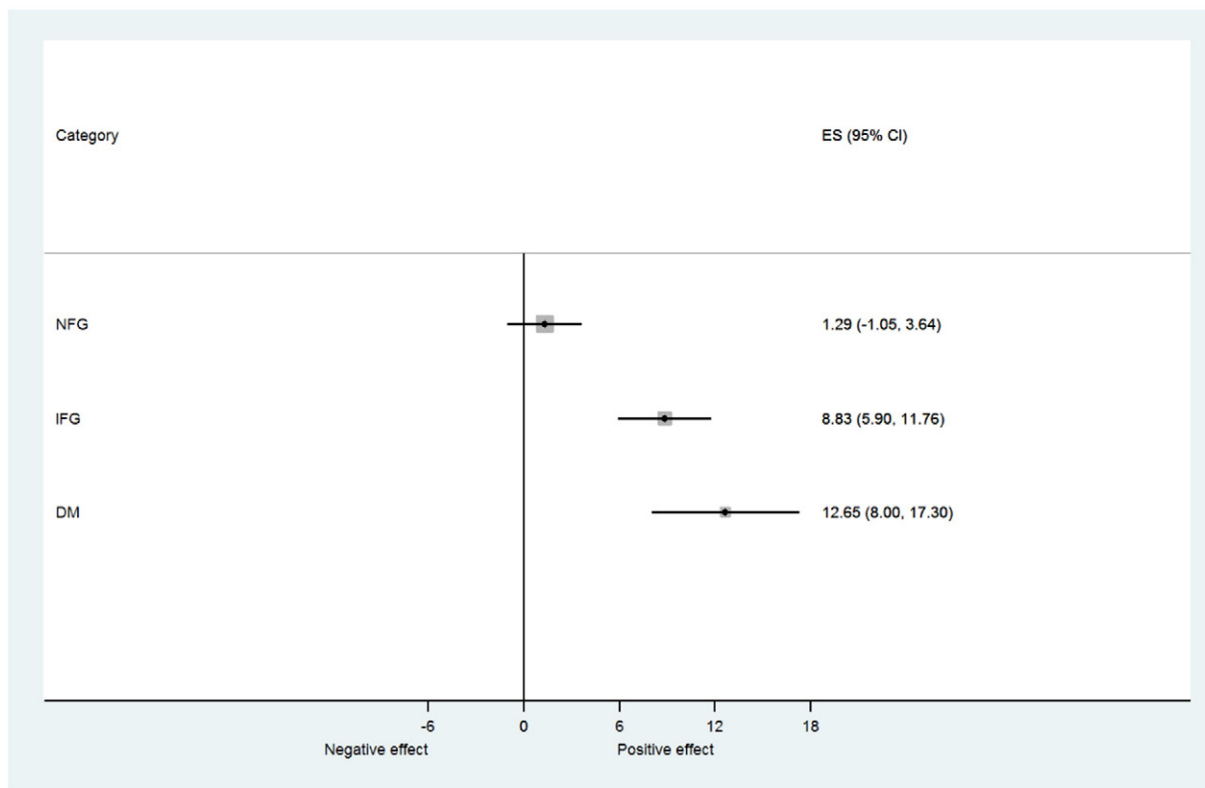
Unadjusted mean values of LV cavity dimension and wall thickness were within normal ranges according to ASE and EACVI [23]. Although it remains controversial whether indexing for height, weight, or BSA should be the preferred method, most large population studies reporting LVM have indexed for BSA, prompting us to use this as our indexing term as well. The reported prevalence of LVH detected by echocardiography in the general population is 5–20% [2,27,28], whereas in patients with established DM, prevalence estimates vary between 20 and 70% [3,29,30], depending primarily on age and the diagnostic criteria used. Keeping in mind the exclusion of subjects with known cardiovascular disease and/or use of cardiovascular, anti-diabetic, or lipid-lowering therapy in the present study, our demographics were in agreement with previous similar studies.

In individuals without overt cardiovascular comorbidities, greater age, SBP, BMI, DM, and ethnicity have been identified as independent risk factors for increased LVMI [8–17]. LVMI is also greater in men, independently of body size [23], and NT-proBNP levels are significantly higher among subjects with LVH than those without, after adjustment for blood pressure [31]. Our results were compatible herewith, as higher age, SBP, BMI, NT-proBNP, DM, and male sex were all significantly associated with greater LVMI, at least on univariable analysis.

4.2. Left ventricular mass and relative wall thickness

The effect of categorized FPG or IFG per se on LVM after covariate adjustment has been evaluated in two subsamples from the *Strong Heart Study*. De Marco et al. [19] showed that obese adolescent and young adult individuals with IFG or DM exhibited progressively higher LVMI and RWT than subjects with NFG, whereas Capaldo et al. [32] found greater LVMI and RWT in subjects, who had either isolated IFG or combined IFG and IGT on an oral glucose tolerance test (OGTT). The odds of LVH was significantly greater among individuals with both IFG and IGT than those with IFG only, and the differences were more apparent in female subjects. Supportive of these findings, independent associations between IGT and LV wall thickness and LVM were also demonstrated

a



b

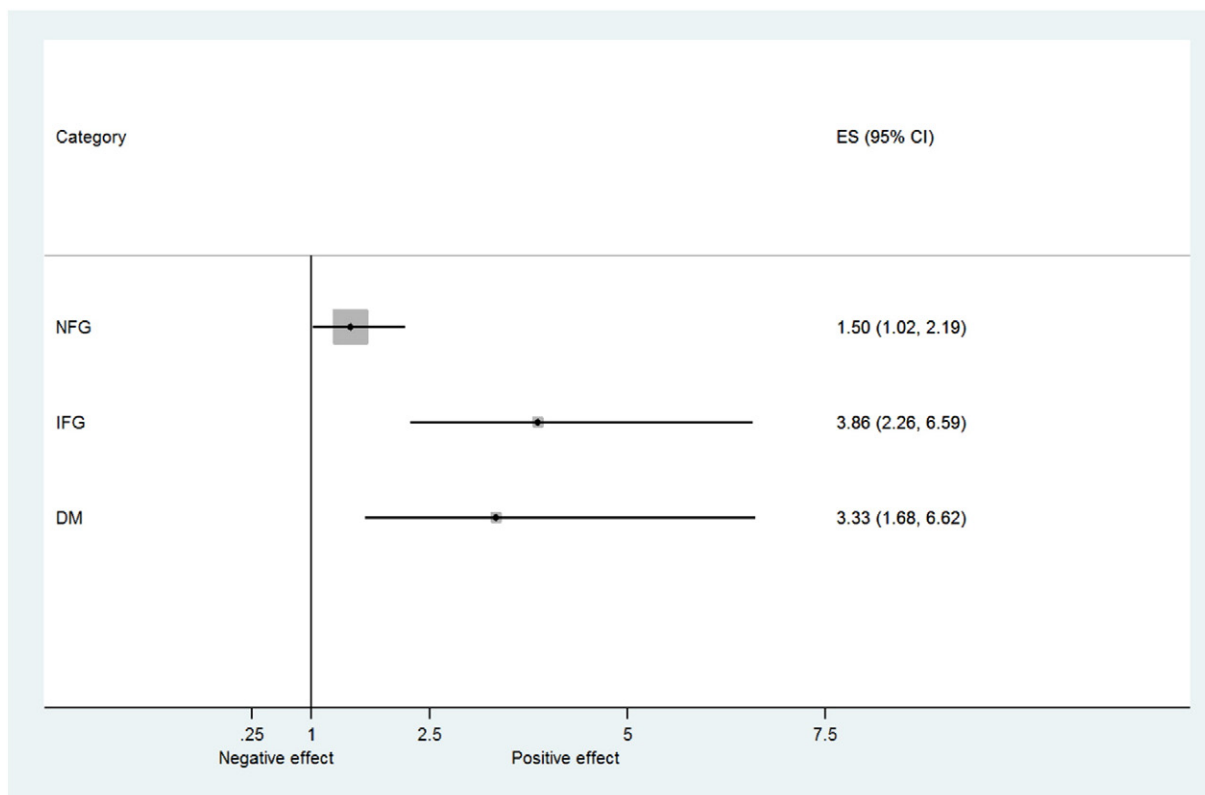


Fig. 2. a: Forest plot showing the interaction between FPG category and NT-proBNP in the prediction of LVMI. ES: estimate; CI: confidence interval. b: Forest plot showing the interaction between FPG category and NT-proBNP in the prediction of LVH. ES: estimate; CI: confidence interval.

Table 3b

Binary logistic regression model for the prediction of left ventricular hypertrophy (pseudo- $r^2 = 0.126$).

| Risk factor | Odds ratio (OR) (95% CI) | P-value |
|--|--------------------------|----------|
| Age (per year) | 1.05 (0.999 to 1.11) | 0.054 |
| Female sex | 1.46 (0.87 to 2.47) | 0.15 |
| Body mass index (per kg/m ²) | 1.08 (1.01 to 1.16) | 0.04 |
| Systolic blood pressure (per mmHg) | 1.02 (1.004 to 1.03) | 0.009 |
| Log(NT-proBNP) (per log(pmol/L)) | 1.88 (1.39 to 2.56) | < 0.0001 |
| Fasting plasma glucose (FPG) category | | |
| Normal fasting glucose (NFG) (reference) | | |
| Impaired fasting glucose (IFG) | 1.26 (0.72 to 2.21) | 0.4 |
| Diabetes mellitus (DM) | 0.86 (0.41 to 1.80) | 0.7 |

Log(HDL-cholesterol) was significantly associated with the presence of left ventricular hypertrophy in univariable analysis only.

in both the *Strong Heart Study* [20] and the *Framingham Heart Study* [18], with the relations in the latter being stronger for women than for men. Contrary to the above, but concordant with the *Multi-Ethnic Study of Atherosclerosis* [33], we were unable to detect a graded association between FPG category and LVMI, presence of LVH, or RWT. Additionally, there was no significant interaction between sex and FPG category. There are, however, several potential explanations for these discrepancies between studies. Firstly, although the risk of future development of type 2 DM is the same for individuals with either isolated IFG or IGT, the overlap between these categories is very limited. The prevalence of IGT is higher in women than in men, whereas the converse is true for IFG; and IGT is a stronger predictor of cardiovascular mortality than is IFG [34]. Furthermore, the development of adverse myocardial changes may require long-term exposition to elevated glucose levels, and the time period of glucometabolic disturbances in the present cohort would expectedly be short. Secondly, data from the *Strong Heart Study* referred to a specific ethnic cohort, i.e. American Indians, which may limit the generalizability to prediabetic individuals from different ethnicities. Thirdly, as discussed in the following section, the importance of impaired glucose metabolism may decrease with age, and the subjects in the present study were on average older than those examined by De Marco et al. (14–39 years) and Capaldo et al. (46–65 years), respectively.

4.3. Important interactions

FPG category significantly interacted with the association between age and the presence of concentric remodeling, i.e. higher age was predominantly associated with concentric remodeling in subjects without DM. This may be explained by the *Cardiovascular Continuum*, i.e. the concept that both physiological and pathological aging brought on by cardiovascular risk factors, e.g. DM, result in similar disturbances in LV structure and function [35–37]. Therefore, impaired glucose metabolism can be considered an accelerator for physiological aging. Since both age and impaired glucose metabolism are known risk factors for concentric LV changes [14–16,18,20], one would expect the effect of FPG category to be weaker in older subjects and vice versa. Supporting this hypothesis, we found that when the study population was split according to median age, the association between the presence of either IFG or DM and concentric LV remodeling was stronger and primarily positive in only the younger study subjects (odds ratio for younger half: 1.56 (95% CI: 0.91 to 2.67), $p = 0.11$; odds ratio for older half: 0.77 (95% CI: 0.48 to 1.23), $p = 0.28$; $p = 0.053$ for interaction).

In addition, there was a significant interaction between FPG category and NT-proBNP, i.e. higher NT-proBNP was predominantly associated with greater LVMI and presence of LVH among subjects with IFG or DM. This finding could be explained by the following observations: 1) Subjects with IFG and DM had greater BMI than subjects with NFG, and there is a known inverse relationship between BMI and BNP, which may further be augmented by the presence of DM and other components of the metabolic syndrome [38,39]; 2) Subjects with

untreated DM, but not IFG, had greater LVMI, RWT, and worse diastolic function, which are all associated with higher NT-proBNP [31,40–42]. In other words, a plausible, although speculative interpretation may be that the association between NT-proBNP and LV size merely appeared stronger among subjects with IFG due to lower NT-proBNP, whereas among subjects with untreated DM, the stronger association resulted from both low circulating NT-proBNP levels and adverse LV changes. In fact, increased production of natriuretic peptides may precede echocardiographically silent structural and functional changes, and these early alterations of myocardial composition in DM might be mediated by changes in the coronary microcirculation, i.e. decreased coronary flow reserve, leading to cell injury and reactive fibrosis [43–45].

4.4. Potential clinical implications

In the present study, DM was mainly associated with concentric LVH as well as diastolic dysfunction, and of all the LV geometric patterns, concentric LVH displayed the strongest correlation with diastolic dysfunction. As previously mentioned, subjects with concentric LVH may be at greater risk of morbidity and mortality than subjects with other LV geometric patterns [5–7]. Moreover, antihypertensive treatment for LVH regression seems less effective among patients with established DM [46,47], and the role of tight glycemic control among patients with type 2 DM remains unproven. Formation of advanced glycation end products and their cross-linking with collagen in patients with DM may perhaps account for this therapeutic failure [48]. Therefore, in DM, the presence of LVH could possibly represent a more deleterious form of LVH than seen in other conditions. Since the adverse myocardial alterations in DM might be consequences of prolonged exposure to hyperglycemia and/or obesity, the presence of IFG may provide a window of opportunity to prevent or reduce LVH and the associated diastolic dysfunction by halting progression into overt DM.

4.5. Limitations

Despite the relatively high participation rate of 72% in MPP-RES, one could still argue that the study subjects did not represent a truly random population sample since people who agree to take part may be healthier than the general population. The applicability of the results in females may be limited by the fact that 70% of subjects in the present study were male, and the generalizability to groups other than middle-aged to elderly Caucasians is unknown as well. Furthermore, our exclusion of more than half of the original study population in order to get a cohort of apparently healthy subjects in whom possible associations were not affected by medication may have introduced a selection bias. The subgroup division was mainly based on single FPG measurements. The addition of an OGTT and/or HbA_{1c} measurements would have been desirable, as IGT and DM defined by OGTT are more common among women than men, whereas IFG is more common among men [34], and HbA_{1c} provides an estimate of the average glucose levels, and perhaps sustained myocardial affection, over a 8–12 week period [49]. The oversampling of subjects with either IFG or DM also prevented us from using FPG as a continuous variable.

Although 2D-guided linear LV measurements have adverse prognostic value and are feasible, especially when studying large populations, a number of potential limitations deserve mentioning [23]: The method is based solely on basal dimensions and unable to accommodate for LV shape and size changes that might occur along the long axis of the chamber, and the formula for calculating LVM assumes normal LV geometry and cubes the linear measurements. Therefore, even small errors or, for example, discrete upper septal thickening (DUST), which is particularly common in elderly, hypertensive subjects [50], may significantly influence the calculated mass. We assumed; however, that excluding subjects with reduced LVEF $\leq 50\%$ would largely account for distorted LV geometry except DUST. Lastly, the cross-sectional nature of our study prevents us from making finite inferences about causality,

including the inability to assess the impact of exposure duration, e.g. incidentally discovered DM and hypertension, on outcome.

5. Conclusion

In conclusion, although apparently healthy, elderly subjects with untreated DM had higher values of LVMI and a greater prevalence of concentric LVH, the associations were not independent of other risk factors. However, FPG category significantly interacted positively with the association between NT-proBNP and LV size, with NT-proBNP predominantly being associated with greater LV size in subjects with IFG or DM.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcme.2015.10.005>.

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